PostScript

CORRESPONDENCE

Anti-GQ1b IgG antibody syndrome: clinical and immunological range

We read with interest the article by Odaka *et al*.[1] In this article, the authors attempted to establish a nosological relation between Miller Fisher syndrome, Guillain-Barré syndrome with ophthalmoplegia, Bickerstaff's brain stem encephalitis, and acute ophthalmoparesis without ataxia on the basis of anti-GQ 1b IgG antibody. The retrospective study included only those patients who were positive for anti-GQ1b IgG antibody, whose clinical range was subsequently evaluated. This introduces a selection bias, as there was no reference to those patients who may have had these diseases with ophthalmoparesis and yet do not have this particular antibody in their serum. Thus, this inherently flaws the attempt to establish these entities as a clinical range, as there may be other antibodies detected in these other patients.

Because there is no specific diagnostic criteria established for Miller Fisher syndrome, Bickerstaff's brain stem encephalitis, and acute ophthalmoparesis, the authors have used their own diagnostic criteria for the purpose of the study to classify the patients. The criteria set down for diagnosis do satisfy the minimum prerequisites required to diagnose the conditions as defined in previous reports on these clinical entities.[2 3] However, the inclusion of the presence of anti-GQ1b IgG antibody as a supportive feature for diagnosis is the authors' bias in these criteria.

It has been established in previous immunological studies that the patients with anti-GQ1b IgG antibody presented with varying combinations of ophthalmoparesis, ataxia, areflexia, or altered sensorium.[4] However, without studying the clinical and immunological profile of other patients with Miller Fisher syndrome, Bickerstaff's brain stem encephalitis, and Guillain-Barré syndrome with ophthalmoplegia and acute ophthalmoparesis without ataxia who do not demonstrate anti-GQ1b IgG antibody in the serum, it would be fallacious to use the term "anti-GQ1b IgG antibody syndrome". The association of anti-GQ1b IgG antibody has been established with 88%–89% concordance in those with Miller Fisher syndrome,[5] but whether patients with Miller Fisher syndrome, Guillain-Barré syndrome with ophthalmoplegia, acute ophthalmoparesis without ataxia, and Bickerstaff's brain stem encephalitis without anti-GQ1b antibody have a similar or different clinical profile and other associated antibodies needs to evaluated. Only then can the knowledge of association of anti-GQ1b IgG antibody be extrapolated to the clinical range.

Grouping these patients into an antibody syndrome also does not help in deciding therapy as patients without this antibody may respond equally well to plasmapheresis, due to the presence of other recognised or unrecognised antibodies. Therefore, patients presenting with Miller Fisher syndrome, Bickerstaff's brain stem encephalitis or Guillain-Barré syndrome should be given the benefit of plasmapheresis and intravenous immunoglobulins, irrespective of he presence of anti-GQ1b IgG antibody in the serum.

In conclusion, although the authors have probed an important association of anti-GQ1b IgG antibody with some cases of Miller Fisher syndrome, Guillan-Barré syndrome with ophthalmoplegia, Bickerstaff's brain stem encephalitis, and acute ophthalmoparesis without ataxia, it cannot lead us to make a syndromic diagnosis clinically and infer about therapy.

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Authors' reply

Those patients showing either consciousness disturbance (coma, semicoma, or stupor) or pyramidal signs (hyperreflexia or pathological reflexes) were diagnosed as "Bickerstaff's brain stem encephalitis" in our article.[1] One of the authors, however, has proposed that "brain stem encephalopathy of Bickerstaff type" or "Bickerstaff's encephalopathy" is an appropriate diagnosis for such patients.[2] The lack of definite inflammatory changes in the brain stem in two necropsied cases reported by Bickerstaff's group suggests the term *encephalopathy*, not *encephalitis*. We therefore use the term "Bickerstaff's encephalopathy" in this reply.

Panda and Tripathi misunderstand what we described. We did not intend the term "anti-GQ1b IgG antibody syndrome" to be used as a clinical diagnosis, which was clearly stated in the conclusion of the abstract of our article.[1] We mentioned that recognition of this syndrome is useful for understanding the aetiological relation among Miller Fisher syndrome, Guillain-Barré syndrome, Bickerstaff encephalopathy, and acute ophthalmoparesis without ataxia. Willison's group have shown the pathogenic effects of anti-GQ1b IgG antibody in an ex vivo model.[3] Their excellent studies provide us with theoretical backing that the removal of anti-GQ1b antibodies is reasonable. Recognition of the anti-GQ1b IgG antibody syndrome, therefore, is useful for introducing the established treatments of Guillain-Barré syndrome (plasma exchange and intravenous immunoglobulins) for use with the other conditions. Although acute paresis of extraocular muscles is a cardinal sign among each condition, the reason why the clinical presentations differ remains to be elucidated.

Several groups, including ours, have reported that some patients with Miller Fisher syndrome, Guillain-Barré syndrome with ophthalmoplegia, Bickerstaff's encephalopathy, and acute ophthalmoparesis have anti-GQ1b IgG antibody during the acute phase of the illness. Not all the patients with each condition have this autoantibody, even those with Miller Fisher syndrome. The presence of seronegative patients indicates that pathogenesis of each condition (even Miller Fisher syndrome) is heterogeneous. Because the purpose of our study was to clarify the nosological relation among each condition, we reviewed medical records of 194 patients with anti-GQ1b IgG antibody, and diagnosed them.[1] This step enabled each condition to be more homogenous, then it became more easy to judge whether a clinical and immunological continuity exists among those conditions. That is one way to elucidate the nosological relation among each condition which has heterogenous pathogenesis, although Panda and Tripathi thought that selection bias existed in our study. As disclosed in patients with myasthenia gravis without antiacetylcholine receptor antibody,[4] novel autoantibodies may be found in seronegative patients with Miller Fisher syndrome. If the novel autoantibodies are detected in the other conditions as well, our hypothesis that each condition forms a continuous range will be supported.

Another way to clarify the nosological relation is shown. Irrespective of the presence or the absence of the anti-GQ1b IgG antibody, for example, we investigated clinical and immunological continuity of 62 patients with Bickerstaff's encephalopathy with (n=37) and without (n=25) limb weakness.[5] There was no significant difference in the clinical features except limb weakness between Bickerstaff's encephalopathy with and without limb weakness. Both conditions therefore may be closely related, and form a continuous range. The results give further support to the idea that Bickerstaff's encephalopathy and Guillain-Barré syndrome form a continuous range. In a large series, moreover, we will report whether clinical and immunological continuity exists among Fisher syndrome, Bickerstaff's encephalopathy, and Guillain-Barré syndrome. In these studies, we will analyze whether clinical presentations differ between seropositive and seronegative patients in each condition. Here we show the preliminary results obtained in Bickerstaff's encephalopathy (table 1). Anti-GQ1b IgG antibody was present in 15 (60%) of the 25 patients with Bickerstaff's encephalopathy. There was no significant difference in the clinical features including the presence of antecedent infections between the seropositive and seronegative patients (p=0.8; post hoc test). These results suggest that an autoimmune mechanism may function in the development of seronegative Bickerstaff's encephalopathy as well.

Panda and Tripathi also misunderstand the point of treatment. We insisted that established treatment for Guillain-Barré syndrome might be more readily introduced as

Table 1 Clinical profiles in patients with Bickerstaff's encephalopathy with or without anti-GQ1b IgG antibody

	Anti-GQ1b IgG			
	Positive		Negative	
Number of patients	15		10	
Sex (M/F)	10/5		7/3	
Median age (range)	52 (17–63)		48 (3–91)	
	n	%	n	%
Antecedent illness:				
Upper respiratory infection	8	53	7	70
Diarrhoea	2	13	0	0
Initial symptoms:				
Diplopia	8	53	5	50
Consciousness disturbance	4	27	2	20
Gait disturbance	3	20	4	40
Blepharoptosis	2	13	0	0
Photophobia	1	7	0	0
Dysesthesia	0	0	2	20
Dysarthria	0	0	1	10
Neurological signs during the course of the illness:				
Consciousness disturbance				
Drowsiness	4	27	9	90
Stupor, semicoma, or coma	3	20	1	10
Blepharoptosis	4	27	4	40
External ophthalmoplegia	15	100	10	100
Internal ophthalmoplegia	6	40	1	10
Nystagmus	8	53	3	30
Facial weakness	5	33	2	20
Bulbar palsy	2	13	2	20
Tendon reflex				
Brisk	7	46	3	30
Normal	1	7	3	30
Decreased	3	20	1	10
Absent	4	27	3	30
Babinski's sign	4	27	3	30
Ataxia	15	100	10	100
Deep sense impairment	0	0	1	10
Superficial sense impairment	1	7	2	20

the treatment for anti-GQ1b IgG antibody syndrome.[1] We think that the treatment should be given for seronegative patients with Fisher syndrome and Bickerstaff's encephalopathy, although we should rule out similar conditions such as Wernicke's encephalopathy, vascular disease involving the brain stem, multiple sclerosis, neuro-Behçet's disease, botulism, myasthenia gravis, brain stem tumour, and pituitary apoplexy, which are listed in table 1 of our article.[1]

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Parkin gene related neuronal multisystem disorder

We read with much interest the article on Japanese patients with parkin gene related autosomal recessive juvenile parkinsonism (ARJP) complicated by cerebellar and pyramidal tract dysfunction.[1] Recently, we described a Dutch family with parkin gene related ARJP showing typical levodopa responsive parkinsonism. The proband clinically had additional mild gait ataxia and pathologically showed—besides classic parkin gene related ARJP findings—neuronal loss in parts of the spinocerebellar system—namely, Purkinje cell layer, dentate nucleus, and gracile fascicles.[2] Just as our Japanese colleagues, we suspected some kind of hereditary multiple system degeneration with predominant parkinsonism until genetic analysis indicated parkin gene related ARJP. Although the non-extrapyramidal abnormalities in the Japanese and in our patients could have been coincidental, the recent Japanese findings seem to confirm that the spinocerebellar and probably also other systems can be affected in parkin gene related ARJP. The fact that the Japanese patients did not respond to levodopa may have very important clinical consequences because it suggests that neurologists have to request an analysis of the parkin gene in patients with autosomal recessive levodopa non-responsive parkinsonism accompanied by a multisystem disorder.

The authors found identical parkin gene mutations in two unrelated families—namely, deletions extending from exons 3 to 4. Although it is very striking that two unrelated Japanese families showed identical genetic abnormalities, the degeneration of non-extrapyramidal systems is not exclusively related to these particular genetic abnormalities because our compound heterozygous patients showed clearly different mutations—that is, a heterozygous transversion Lys211Asn in exon 6 and a heterozygous deletion of exon 3. Furthermore, as Kuroda *et al*[1] remarked themselves, other patients with similar parkin gene mutations to Kuroda's patients did not show non-extrapyramidal abnormalities, so the genotype-phenotype relation in parkin gene related ARJP remains to be elucidated. However, taken together the findings of Kuroda *et al*[1] and of our own, it seems very probable that the symptoms of parkin gene related ARJP are not necessarily restricted to parkinsonism but can also include signs and symptoms of a neuronal multisystem disorder.

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Authors' reply

Since the first report of autosomal recessive juvenile parkinsonism (ARJP),[1] it has been established as a clinical entity on the basis of age at onset (usually before the age of 40), clinical features and neuropathological findings. The clinical symptoms include homogeneous features such as typical signs of parkinsonism (rigidity, tremor, akinesia), foot dystonia, diurnal fluctuations, sleep benefit, hyperreflexia, a striking response to levodopa, and early susceptibility to levodopa induced dyskinesia.[2 3] Levodopa responsive parkinsonism is recognised as one of the most important features of ARJP. However, in 1994 we reported on two Japanese patients from a family with autosomal recessive parkinsonism complicated with multiple system degeneration.[4] The patients exhibited symptoms corresponding to cerebellar and pyramidal tract dysfunctions as well as nigrostriatal dysfunction, and the most prominent feature in the patients was parkinsonism not responsive to levodopa, indicating dysfunction in both nigral dopaminergic neurons and the striatum. The clinical features were sharply contrastive to those in patients with ARJP;